

- 44 -

WHAT IS CLAIMED IS:

- 5 1. A pharmaceutical composition comprising a KGF agonist and a gastrin compound that provides beneficial effects relative to each compound alone, and optionally a pharmaceutically acceptable carrier, excipient, or vehicle.
- 10 2. A pharmaceutical composition as claimed in claim 1 that provides sustained beneficial effects.
- 15 3. A pharmaceutical composition as claimed in claim 2 in a form that provides normal blood glucose levels in a subject that persist for a prolonged period of time after administration.
- 20 4. A pharmaceutical composition as claimed in any preceding claim comprising therapeutically effective amounts of a KGF agonist and a gastrin compound in a form for chronic or acute therapy of a subject in need thereof.
- 25 5. A pharmaceutical composition as claimed in claim 4 wherein the therapeutically effective amounts are suboptimal relative to the amount of each compound administered alone for treatment of diabetes.
- 30 6. A pharmaceutical composition as claimed in any preceding claim wherein the ratio of KGF agonist to gastrin compound is selected to augment the activity of the KGF agonist or gastrin compound.
- 35 7. A pharmaceutical composition as claimed in claim 6 wherein the ratio of a KGF agonist to a gastrin compound is from about 1:1 to 1:110, 1:1 to 1:100, 1:1 to 1:75, 1:1 to 1:50, 1:1 to 1:25, 1:1 to 1:10, 1:1 to 1:5, and 1:1.
- 40 8. A pharmaceutical composition as claimed in claim 6 wherein the ratio of a gastrin compound to a KGF agonist is from about 1:1 to 1:110, 1:1 to 1:100, 1:1 to 1:75, 1:1 to 1:50, 1:1 to 1:25, 1:1 to 1:10, and 1:1 to 1:5.
9. A pharmaceutical composition as claimed in any preceding claim wherein the KGF agonist is used in combination with the gastrin compound at therapeutically effective weight ratios of between about 1:1.5 to 1:150, preferably 1:2 to 1:50.
10. A pharmaceutical composition as claimed in any preceding claim wherein the KGF agonist and the gastrin compound are present in doses that are at least about 1.1 to 1.4, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, or 10 fold lower than the doses of each compound alone required to treat a disease or condition.
11. A pharmaceutical composition as claimed in claim 1 comprising an additive amount or synergistically effective amount of the KGF agonist and the gastrin compound in a pharmaceutically acceptable excipient, carrier, or vehicle.
12. A pharmaceutical composition as claimed in claim 1 comprising between 0.1 to 20, 0.1 to 30, 0.1 to 40, 0.1 to 50, and 0.1 to 60 micrograms/kg/day KGF agonist and 0.1 to 20, 0.1 to 30, 0.1 to 40, 0.1 to 50, and 0.1 to 60 micrograms/kg/day gastrin compound.

- 45 -

13. A pharmaceutical composition as claimed in claim 2 wherein the beneficial effects are one or more of the following: reduced or absent islet inflammation, decreased disease progression, increased survival, or decreased symptoms of a disease or condition.
- 5 14. A pharmaceutical composition as claimed in any preceding claim wherein the beneficial effects are sustained beneficial effects that persist for a prolonged period of time after termination of treatment.
- 10 15 16. A pharmaceutical composition as claimed in claim 13 wherein the beneficial effects are sustained for at least about 2 to 4 weeks, 2 to 8 weeks, 2 to 12 weeks, 2 to 24 weeks, 2 weeks to 12 months, and 2 weeks to 18 months following treatment.
17. A pharmaceutical composition as claimed in any preceding claim wherein the sustained beneficial effects may manifest as increased C-peptide production, increased pancreatic insulin production, and about normal or low blood glucose levels for a prolonged period following treatment.
18. A pharmaceutical composition as claimed in any preceding claim wherein the beneficial effect is at least about a 0.05%, 0.1%, 0.5%, 1%, 2%, 5%, 10%, 15%, 20%, 20% 30%, 33%, 35%, 40%, 45%, or 50% increase in pancreatic insulin levels.
- 25 19. A pharmaceutical composition as claimed in any preceding claim wherein the beneficial effect is at least about a 2%, 5%, 10%, 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% decrease in blood glucose levels.
- 20 21. A pharmaceutical composition as claimed in any preceding claim wherein the beneficial effect is a decrease in blood glucose levels for a period of at least about about 2 to 4 weeks, 2 to 8 weeks, 2 to 12 weeks, 2 to 24 weeks, 2 weeks to 12 months, and 2 weeks to 18 months following treatment.
- 25 30 22. A pharmaceutical composition as claimed in any preceding claim wherein the KGF agonist is a KGF, KGF-2, fragments, analogs, and derivatives thereof, and active metabolites and prodrugs of KGF.
- 35 23. A method for preventing and/or treating a condition or disease in a subject comprising administering to the subject a therapeutically effective amount of at least one KGF agonist and a gastrin compound to produce a sustained beneficial effect.
24. A method of treatment comprising administering to a subject a therapeutically effective amount of at least one KGF agonist in combination with administration of at least one gastrin compound which upon administration to a subject with symptoms of diabetes provides sustained beneficial effects.

- 46 -

25. A method as claimed in claim 24 wherein administration with of at least one KGF agonist in combination with administration of at least one gastrin compound provides sustained beneficial effects of at least one symptom of diabetes.
- 5 26. A method as claimed in claim 24 wherein therapeutically effective amounts of the KGF agonist and the gastrin compound are combined prior to administration to the subject.
- 10 27. A method as claimed in claim 24 wherein therapeutically effective amounts of the KGF agonist and the gastrin compound are administered to the subject sequentially.
28. A method as claimed in any preceding claim wherein therapeutically effective amounts of a KGF agonist and a gastrin compound are administered at a physiologically acceptable pH.
- 15 29. A conjugate comprising a KGF agonist linked to a gastrin compound to provide beneficial effects, in particular sustained beneficial effects.
30. A method of preparing a stable pharmaceutical composition of a KGF agonist comprising mixing a KGF agonist, a gastrin compound, and a pharmaceutically acceptable carrier, excipient, or vehicle effective to physically stabilize the KGF agonist and adapted to provide beneficial effects preferably sustained beneficial effects.
- 20 31. A method of treating a condition or disease comprising administering a therapeutically effective amount of a KGF agonist and a gastrin compound, or a composition or conjugate of any preceding claim to a subject in need thereof to thereby produce beneficial effects, preferably sustained beneficial effects.
- 25 32. A method of treating a condition or disease comprising administering a KGF agonist and a gastrin compound, or a composition or conjugate of any preceding claim with a plurality of cells to a subject in need thereof to thereby produce beneficial effects, preferably sustained beneficial effects.
- 30 33. A method for treating a subject with a condition or disease comprising contacting *ex vivo* a plurality of cells with a KGF agonist and a gastrin compound, or a composition or conjugate of any preceding claim, optionally culturing the cells, and administering the cells to the subject in need thereof.
- 35 34. A method of any preceding claim wherein the condition or disease is dyslipidemia, hyperglycemia, severe hypoglycemic episodes, stroke, left ventricular hypertrophy, arrhythmia, bacteraemia, septicaemia, irritable bowel syndrome, functional dyspepsia, diabetes, catabolic changes after surgery, stress induced hyperglycemia, gastric ulcers, myocardial infarction, impaired glucose tolerance, hypertension, Alzheimer's disease and other central and peripheral neurodegenerative conditions chronic heart failure, fluid retentive states, metabolic syndrome and related diseases, and disorders and obesity.
- 40 35. A method for inducing islet neogenesis in a subject comprising contacting islet precursor cells with a KGF agonist and a gastrin compound, or a composition, or

- 47 -

conjugate of any preceding claim in a sufficient amount to increase proliferation of islet precursor cells in the subject thereby inducing islet neogenesis.

5 36. A method for expanding and differentiating stem cells into insulin secreting cells comprising contacting the stem cells with an effective amount of a KGF agonist and a gastrin compound or a composition or conjugate of any preceding claim.

10 37. Use of a composition comprising a combination of at least one KGF agonist and at least one gastrin compound for the preparation of a medicament for the treatment of a condition or disease.

15 38. A use of claim 37 wherein the condition or disease is dyslipidemia, hyperglycemia, severe hypoglycemic episodes, stroke, left ventricular hypertrophy, arrhythmia, bacteraemia, septicaemia, irritable bowel syndrome, functional dyspepsia, diabetes, catabolic changes after surgery, stress induced hyperglycemia, gastric ulcers, myocardial infarction, impaired glucose tolerance, hypertension, Alzheimer's disease and other central and peripheral neurodegenerative conditions chronic heart failure, fluid retentive states, metabolic syndrome and related diseases, and disorders and obesity.

20 39. A kit form of a composition or conjugate as claimed in any preceding claim.

25 40. A method for preventing and/or treating diabetes, the method comprising administering to a mammal in need thereof a composition comprising a combination of a KGF receptor ligand and a gastrin /CCK receptor ligand, in an amount sufficient to increase the number of pancreatic insulin secreting β cells in the mammal, thereby preventing and/or treating the diabetes.

30 41. A method for preventing and/or treating diabetes, the method comprising administering to a mammal in need thereof a composition comprising a combination of a KGF receptor ligand and a gastrin /CCK receptor ligand, in an amount sufficient to increase proliferation of islet precursor cells in pancreatic tissue, thereby preventing and/or treating the diabetes.

35 42. A method for preventing and/or treating diabetes, the method comprising: contacting *ex vivo* a plurality of cells with a composition comprising a KGF receptor ligand and a gastrin/CCK receptor ligand in an amount sufficient to increase proliferation of islet precursor cells and the amount of insulin secreting islet cells; and administering the contacted plurality of cells to a mammal in need thereof, thereby preventing and/or treating the diabetes.

40 43. A method of claim 42, wherein the amount of KGF in the composition is substantially lower than the minimum effective dose of KGF required to reduce blood glucose in the diabetic mammal in the absence of a gastrin/CCK receptor ligand.

44. A method for preventing and/or treating diabetes, the method comprising administering to a mammal in need thereof a composition comprising a combination of a KGF receptor ligand and a gastrin /CCK receptor ligand, in an amount sufficient to increase the number of pancreatic insulin secreting β cells in the mammal; and

- 48 -

determining the amount of islet neogenesis, thereby preventing and/or treating the diabetes.

5 45. A method of claim 44, wherein determining the amount of islet neogenesis is measuring a parameter selected from the group of: blood glucose, serum glucose, blood glycosylated hemoglobin, pancreatic β cell mass, serum insulin, pancreatic insulin content, and morphometrically determined β cell mass.

10 46. A method of claim 45, wherein administering the composition reduces blood glucose compared to blood glucose assayed prior to administering the composition.

15 47. A method of claim 45, wherein administering the composition reduces blood glucose by 50% compared to blood glucose assayed prior to administering the composition.

20 48. A method of claim 45, wherein glycosylated hemoglobin concentration is reduced compared to glycosylated hemoglobin concentration in the control mammal not administered the composition.

25 49. A method of claim 45, wherein serum C peptide insulin concentration is increased compared to serum insulin concentration in the mammal assayed prior to administering the composition.

30 50. A method of claim 45, wherein pancreatic insulin concentration is increased compared to pancreatic insulin concentration in the mammal assayed prior to administering the composition.

35 51. A method of claim 45 wherein the cells are pancreatic ductal cells.

52. A method of claim 45, wherein the KGF receptor ligand and the gastrin/CCK receptor ligand are provided in an amount sufficient to induce differentiation of the pancreatic islet precursor cells into glucose responsive insulin secreting islet cells.

53. A method of claim 45 wherein the KGF receptor ligand and the gastrin/CCK receptor ligand are provided in an amount sufficient to induce differentiation of the pancreatic islet precursor cells into glucose responsive insulin secreting islet cells.

54. A method of claim 45, wherein the composition is provided in an amount sufficient to effect differentiation of pancreatic islet precursor cells in pancreatic tissue into mature insulin secreting islet cells.

55. A method of claim 45, wherein the composition is provided in an amount sufficient to increase proliferation of pancreatic islet precursor cells.

56. A method for inducing pancreatic islet neogenesis in a mammal, the method comprising administering to the mammal a composition comprising a combination of a KGF receptor ligand and a gastrin /CCK receptor ligand, in an amount sufficient to increase proliferation of islet precursor cells in pancreatic tissue, thereby inducing pancreatic islet neogenesis.

57. A method of claim 56, wherein the plurality of cells are multicellular.

58. A method of claim 56 wherein the plurality of cells are delivered systemically to the mammal.

- 49 -

59. A method for inducing pancreatic islet neogenesis in a mammal, the method comprising administering a composition comprising a combination of a KGF receptor ligand and a gastrin /CCK receptor ligand, in an amount sufficient to increase the number of pancreatic insulin secreting β cells in the mammal.
- 5 60. A method for inducing islet neogenesis therapy in a cell of an animal, comprising contacting the cell with a nucleic acid sequence encoding a gastrin/CCK receptor ligand operably linked to an insulin promoter receptor ligand and a nucleic acid sequence encoding a KGF receptor ligand operably linked to a metallothionein promoter.
- 10 61. A method of claim 60, wherein the cell is a germ cell.
62. A method of claim 60, wherein the cell is an autologous cell cultured ex vivo.
- 15 63. A nucleic acid construct comprising a nucleic acid sequence encoding a mammalian KGF receptor ligand operably linked to a heterologous promoter and a nucleic acid sequence encoding a mammalian gastrin/CCK receptor ligand operably linked to a heterologous promoter.
64. A composition comprising a gastrin/CCK receptor ligand and a KGF receptor ligand.
65. A composition of claim 64, in a dosage effective for inducing proliferation of islet precursor cells into an increased amount of mature insulin secreting cells.
- 20 66. A composition of claim 64 in a dosage effective for inducing differentiation of an islet precursor cell into a mature insulin secreting cell.
67. A transgenic animal whose germ cells comprise a nucleic acid sequence encoding a mammalian KGF receptor ligand operably linked to a heterologous promoter and a nucleic acid sequence encoding a mammalian gastrin/CCK receptor ligand operably linked to a heterologous promoter.
- 25 68. A kit for preventing and/or treating diabetes, containing a composition comprising a gastrin/CCK receptor ligand and a KGF receptor ligand, a container, and instructions for use.

30